

## ***Advisory Committee for Pharmaceutical Science, CDER, FDA October 2005***

### **A PhRMA Perspective on Using a Quality-by-Design Approach for Regulatory Decisions in Establishing Meaningful Drug Dissolution/Release Specifications While Creating Flexibility for Continuous Improvement.**

#### **Background**

At the last meeting held in May 2005, the Advisory Committee for Pharmaceutical Science unanimously voted to adopt the tactical steps for implementation of a new Quality-by-Design (QbD) based approach to pharmaceutical quality assurance and control of drug dissolution or release rate characteristics of solid oral drug products.

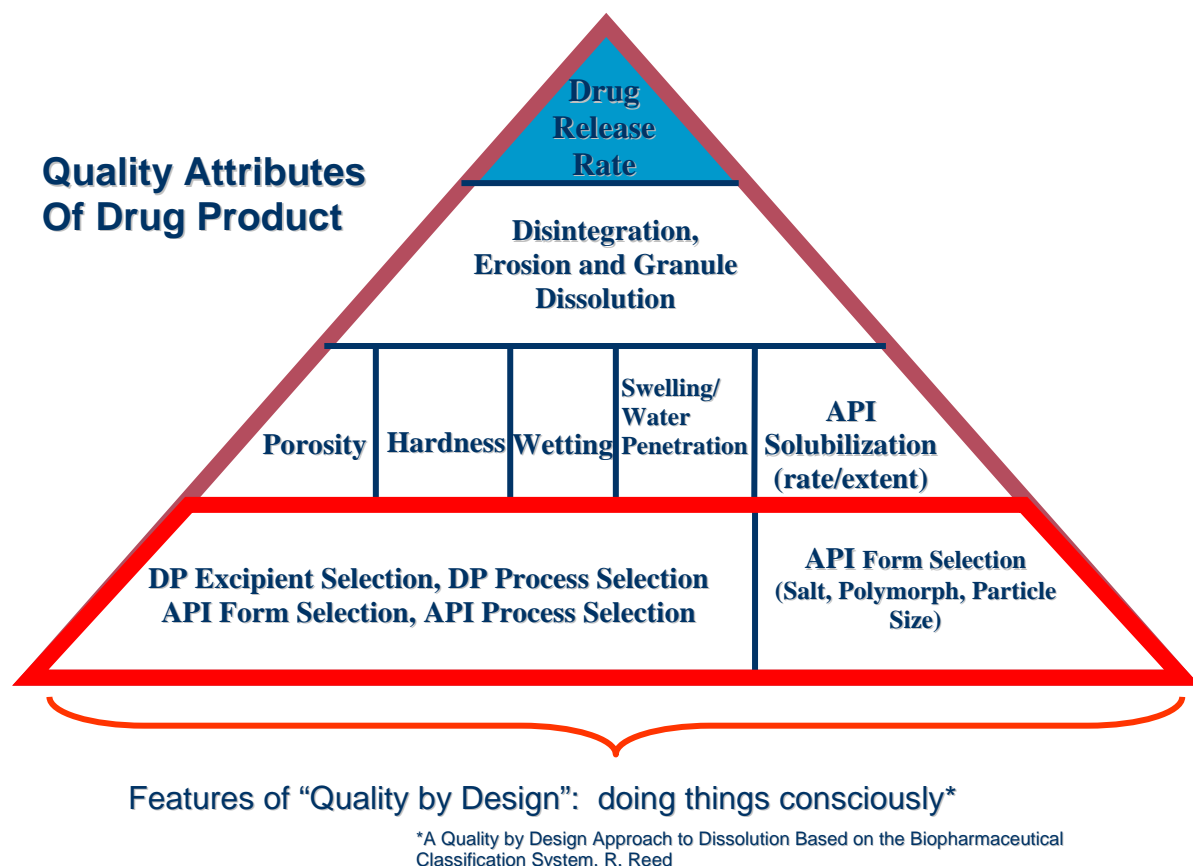
The innovator industry, represented by the Pharmaceutical Research and Manufacturers of America (PhRMA), wishes to confirm its endorsement of the QbD principles being applied for the establishment of meaningful testing to insure drug release. While recognizing that implementation is voluntary and may vary between companies, PhRMA proposes a scientifically based approach to insure the expected drug release of immediate release solid oral dosage forms that is in harmony with ICH Q8 concepts. It is also felt that using a systematic approach of identifying key aspects of the product should not lead to any delays in approval yet may actually facilitate more regulatory flexibility in the implementation of post-approval manufacturing changes.

#### **QbD Applied to Drug Release (Immediate Release Products)**

Alternatives exist through effective applications of QbD principles to ensure needed drug release rate is achieved without developing a dissolution specification. This process begins with understanding the required drug release rate. The approaches to gathering this information can be as sophisticated as advanced modeling of gastrointestinal systems. Alternatively utilizing bio-availability studies that are run throughout the clinical process will help determine release rate needs. Most simply, one can measure dissolution properties of the dosage form used in pivotal clinical studies.

Once these needs are understood, a deconvolution of events and factors affecting the release rate of a drug substance from immediate release dosage forms can be addressed. Because drug dissolution and release is an essential step in delivering the drug to its site of action, it also is a critical quality characteristic that needs to be controlled throughout the shelf-life of a product. We recognize that the science has advanced such that there are opportunities to understand and measure more fundamental attributes of the drug product that determine the drug release rate. These attributes can be designed into the formulation using QbD approaches. The drawing below is meant to illustrate the deeper fundamental and mechanistic understanding that can be gained and designed into the product to ensure the needed drug release rate is achieved. The understanding and

control of these more fundamental attributes becomes the basis for elimination of a dissolution specification.



The approach proposed by PhRMA uses the understanding gained through structured experimental design and understanding to create the relationship between measurable characteristics and justifies their use based on knowledge of the drug substance manufacturing process, drug substance form, excipient selection for drug product and drug product manufacturing process. The use of meaningful measurements can provide reliable means for identifying sources of variability in pivotal clinical materials and also in controlling drug product. This deeper understanding becomes a major improvement over the traditional dissolution specification with its known limitations. The matrix below is an example of how various attributes can be influenced by design choices, via formulation and process factors, by both deploying alternative characterization approaches and leveraging development experience on similar products.

## Connecting QBD to Quality Attributes

| QBD Factors            | Porosity   | Hardness   | Wetting  | Swelling/ Penetration  | API Solubilization   |
|------------------------|--|--|--|--|--|
| DP Excipient Selection | PS of excipients (match to API)<br>Hardness/<br>Brittleness of excipients<br>Granule strength                        | Bonding Index<br>Brittle Fracture Index<br>Compression force profile via simulation<br>Other mechanical properties | Contact angle measurements   | Solubility of excipients<br>Microscopic evaluation of swellability   | Analysis described in porosity, wetting and swelling   |
| DP Process Selection*  | 1 <sup>st</sup> choice: wet granulation<br>2 <sup>nd</sup> choice: dry granulation<br>3 <sup>rd</sup> : direct comp. | 1 <sup>st</sup> choice: dry granulation<br>2 <sup>nd</sup> choice: wet granulation/direct compression              | 1 <sup>st</sup> choice: wet granulation<br>2 <sup>nd</sup> choice: direct comp.<br>3 <sup>rd</sup> : dry granulation | 1 <sup>st</sup> choice: wet granulation<br>2 <sup>nd</sup> choice: direct comp.<br>3 <sup>rd</sup> : dry granulation | 1 <sup>st</sup> choice: wet granulation<br>2 <sup>nd</sup> choice: direct comp.<br>3 <sup>rd</sup> : dry granulation |
| API Form Selection     | PS of API (match to excipients)<br>Hardness/<br>Brittleness of API   | Bonding Index<br>Brittle Fracture Index<br>Compression force profile via simulation<br>Other mechanical properties | Contact angle measurements   | Counter ion selection<br>Polymorph selection<br>Solubility of API form<br>Microscopic evaluation of swellability     | Counter ion selection<br>Polymorph selection<br>Analysis described in porosity, wetting and swelling                 |
| API Process Selection  | N/A  | Crystallization/<br>Milling – mechanical property; shape/size  | Milling  | N/A  | Crystallization/<br>Milling – shape/size   |

\*use DP excipient selection measurements to facilitate DP process selection

### Elements for Implementation

The QbD-based, structured method of pharmaceutical development could ease concerns that industry has about delays in the regulatory process and provide a more rigorous, more risk-averse scientific framework for ascertaining pharmaceutical quality. Essential elements of the type of information that would be items such as:

- Drug substance characteristics such as solubility, stability, ionization and permeability.
- Selection criteria of raw materials such as compatibility justification and intended function.
- Product design considerations such as anticipated or desired dissolution mechanisms and factors based on prior knowledge that could guide product development.

Specific tactical steps discussed by the committee for implementing a QbD approach to quality assurance of dissolution rate include:

- Develop an alternate approach to the current regulatory requirements for dissolution method validation.
- Develop an approach to utilize the pivotal clinical trial product to characterize reproducibility of the measurement system and define criteria when this study can also serve to benchmark “acceptable” total variance.
- Develop a comprehensive decision tree approach for establishing dissolution specifications comparing the new decision tree to the current ICH Q6A [27355] decisions trees and articulate the pros and cons of each.

- Identify opportunities for using the PAT [46176] approach for controlling dissolution rate.
- Develop a decision tree for the “design space” concept articulated in the draft ICH Q8 [48648] to minimize the need for regulatory application commitments on process parameters and manufacturing options.
- For both new and generic drug applications, develop a side-by-side comparison of the proposed regulatory decision process with the current decision process for dissolution specifications and post approval change management.
- Seek recommendations from the ACPS on the general considerations for identifying and developing statistical analysis procedures to support the proposed tactical steps.
- Develop a detailed proposal for the above mentioned tactical steps based on recommendations of the ACPS.
- Work to establish consensus on the detailed regulatory decision criteria at subsequent meetings of the ACPS.
- Seek harmonization on this approach with other regulatory authorities, particularly the ICH regions.